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674522-2001.1**REMARKS**

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance or into better condition for appeal. Consideration and entry of this paper is solicited.

**I. STATUS OF CLAIMS AND FORMAL MATTERS**

Claims 1, 3-5 and 8-11 are pending, claims 1, 5, and 8-10 are amended. Support for the amendments can be found throughout the specification. No new matter is added.

It is submitted that the claims, as originally presented, and as herewith presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. Changes to claims and/or new claims as presented herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these changes are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

**II. THE REJECTIONS UNDER 35 U.S.C. §112, 2<sup>ND</sup> PARAGRAPH, ARE OVERCOME**

Claims 5 and 9-11 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Claim 5 has been amended to recite "a protein agent for inducing vessel maturation", obviating the insufficient antecedent basis rejection. Claim 9 has been amended to remove the recitation of "by admixture" and to clarify the interrelationship between the parts of the kit. The word "inhibitor" has been removed from claim 10. Consequently, reconsideration and withdrawal of the Section 112, second paragraph, rejections is believed to be in order and such action is respectfully requested.

**III. THE REJECTION UNDER 35 U.S.C. §112, 1<sup>ST</sup> PARAGRAPH, IS OVERCOME**

Claim 1 and dependent claims 3-5 and 8-11 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The Office Action alleges that the claims are not enabled for "preventing" atherosclerosis and/or restenosis. Claims 1, 8 and 9 have been rewritten to recite "reducing" atherosclerosis and/or restenosis, as suggested on page 4 of the Office Action. Therefore, reconsideration and withdrawal of the Section 112, first paragraph, rejection is respectfully requested.

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#### IV. THE REJECTION UNDER 35 U.S.C. §103 IS OVERCOME

Claims 1, 3-5 and 8-11 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Inoue *et al.* and Maisonpierre *et al.* in view of Kendall *et al.* and Asahara *et al.* The rejection is traversed.

The Office Action asserts at page 5 that Inoue *et al.* teach that VEGF is involved in the process of atherosclerosis. While they suggest that VEGF "may have some role in the progression of human coronary atherosclerosis", all they actually demonstrate is that VEGF is expressed in atherosclerotic plaques. They do not establish any cause/effect relationship between the presence of VEGF and the occurrence of the plaques.

Further, Kendell *et al.* only show that a VEGF inhibitor can inhibit mitogenesis. It is indeed a significant extrapolation from limited mitogenesis to the reduction or treatment of restinosis or atherosclerosis. In fact, Kendall *et al.* suggest that their invention might be used to treat a variety of diseases and conditions, specifically listing psoriasis, rheumatoid arthritis, hemangiomas, angiofibromas, diabetic retinopathy, neovascular glaucoma and conditions such as tumor vascularization. Nowhere in their disclosure do Kendall *et al.* teach or suggest the use of a VEGF inhibitor to reduce or treat restinosis or atherosclerosis. Further, they do not teach or suggest the combination of a VEGF inhibitor with another molecule generally or an angiopoietin specifically.

Maisonpierre *et al.* report that Ang1 is angiogenic and that Ang2 may antagonize Ang1. Their studies were confined to the expression patterns of Ang1 and Ang2 in mouse embryos and adults; they also performed overexpression studies of Ang2. While they suggest that simultaneous regulation of VEGF and angiopoietins may positively promote revascularization or negatively prevent tumor growth, in no instance do they suggest that the combination can reduce or treat restenosis or atherosclerosis, namely plaque formation, which is not tumor growth.

While Maisonpierre *et al.* may suggest opposing roles for Ang1 and Ang2 in vascularization, Asahara *et al.* conclude that neither Ang1 nor Ang2 alone induce neovascularization. In their mouse corneal neovascularization model, they determined that the combination of VEGF and Ang1 increases vascular density and that the combination of VEGF and Ang2 increases the extent and length of vasculature. They provide no data, teachings or suggestions on the combination of a VEGF inhibitor and angiopoietin.

Further, it is unclear how the skilled artisan could expect a reduction in pathological angiogenesis from either Ang1 or Ang2 alone or in combination with another molecule from the teachings of the cited documents. Alone, they had no effect on neovascularization, and in

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combination with VEGF, both increased vascularization, albeit in different ways. Even considering the state of the art at the time the instant application was filed, it is not obvious that the combination of Ang1 and a VEGF inhibitor would reduce or treat restenosis or atherosclerosis.

Not only do the cited references, alone or in combination, neither teach nor suggest reduction or treatment of restenosis or atherosclerosis using a VEGF inhibitor and an inducer of vessel maturation, they also do not even contain concurring results. If the references cannot agree on the function of the molecules in question, the use of said molecules in treating disease cannot be obvious. Simply, the cited documents lack the necessary incentive or motivation for modifying their teachings to arrive at the instant invention. Further, they fail to provide the necessary suggestion of the desirability of the modification of the teachings, especially as "obvious to try" is not the standard under Section 103, and both the suggestion of an invention and the expectation of its success must be found in the prior art for a proper Section 103 rejection. *See In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993); *In re Fine*, 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988); *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992); *In re Dow*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988).

In sum, the cited references cannot be logically combined since their teachings with respect to the roles of Ang1 and Ang2 do not concur. The combination of the cited documents fails to teach or suggest the administration of VEGF and Ang1 to reduce or treat restenosis and/or atherosclerosis. Rather, the combination of the cited documents leads away from the instant invention because, reading the documents in combination in a light most favorable to the Examiner (without any admission, prejudice, estoppel or the like), the combination of the cited documents may direct the skilled artisan toward the administration of VEGF and Ang1 to promote vascularization or the administration of VEGF and Ang2 to inhibit tumor growth. However, promoting vascularization is contrary to treating restenosis and/or atherosclerosis, as these conditions are not tumors. Thus, what may be suggested by the combination of the cited references is not the instant invention, and in fact, leads away from it. The alleged modification of the documents cited in the Section 103 rejection is untenable in light of the full teachings of the cited documents; and, in view of the case law, the Section 103 rejection cannot stand. Therefore, reconsideration and withdrawal of the Section 103 rejection are requested.

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674522-2001.1CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance, or at least in better condition for appeal. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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674522-2001.1**Version With Markings To Show Changes Made****In the claims:**

1. (Twice Amended) A composition for therapy for reducing[preventing] or treating restenosis and/or atherosclerosis comprising a protein agent for inhibiting VEGF and a protein agent for inducing vessel maturation.
5. (Twice Amended) The composition of claim 3 wherein the protein agent for inducing vessel maturation [inducer] comprises angiopoietin-1.
8. (Amended) A method for reducing[preventing] or treating atherosclerosis or restenosis comprising administering a composition as claimed in claim 1.
9. (Twice Amended) A kit for formulating a composition for reducing[preventing] or treating [atherosclerosis or] restenosis and/or atherosclerosis [as claimed in claim 1 by admixture] comprising a[the] protein agent for inhibiting VEGF and a[the] protein agent for inducing vessel maturation, wherein the agents are in the same container.
10. (Twice Amended) [The kit of claim 9] A kit for formulating a composition for reducing or treating restenosis and/or atherosclerosis comprising a protein agent for inhibiting VEGF and a protein agent for inducing vessel maturation, wherein the agents[protein agent for inhibiting VEGF inhibitor and the protein agent for inducing vessel maturation] are in separate containers.